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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,989	LAUTT, WILFRED WAYNE	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,19 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 12/17/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 1-3, 19, 21-25 are currently pending in this application and are the subject of the Office action.

Information Disclosure Statement

Applicant's information disclosure statement, received 12/17/08, and accompanying copy of the Moncada reference have been considered and made of record.

Response to applicant's arguments/remarks

New Matter rejection under 112, 1st paragraph

This rejection is withdrawn in view of the claim amendment.

Rejection under 112, 2nd paragraph

This rejection is withdrawn in view of the claim amendment.

Rejection under 102(e)

This rejection is withdrawn in view of the claim amendment.

Nonstatutory obviousness-type double patenting - 10/761,596

This rejection is withdrawn in view of the abandonment of copending application No. 10/761,596.

REJECTIONS

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 requires a host to administer the method steps; however, no host is recited. Since an artisan would not be able to practice the instant claim without knowing the specific host to administer the instant claimed method steps, the metes and bounds of the claimed subject matter are unclear. This renders the claimed subject indefinite because the instant claim does not recite a host even though one is required in order to practice the instant claimed method.

Dependent claims 22-25 are rejected for the same reason as these claims fail to correct the deficiency of the claim from which they depend.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 19, and 21-25 are rejected under 103(a) as being unpatentable over Chwalisz et al. (US Patent Application Publication No. 2001/0056068 A1), in view of Herfindal et al. (Herfindal et al. Clinical Pharmacy & Therapeutics. 1992, Chapter 17, pages 307-331, especially page 308, col. 1, 2nd full para. to col. 2, 2nd para.).

The rejection under 112, 2nd paragraph is noted.

Chwalisz et al. (US Patent Application Publication No. 2001/0056068 A1) teach methods for control, management, treatment and prevention of various conditions related to nitric oxide deficiency, including hypertension, cardiovascular disease, osteoporosis, diabetes, male impotence, urinary incontinence, and uterine contractility disorders by administering citrulline or a citrulline analogue, optionally in combination with other enhancing or modulating agents (abstract). Chwalisz et al. teach that nitrovasodilators such as nitroglycerin and sodium nitroprusside (SNP) inhibit vascular

smooth muscle contractility to produce vascular relaxation and to reduce vascular tone and that these compounds release nitric oxide (acting as nitric oxide dononrs) either spontaneously (e.g. SNP) or after metabolic conversion (e.g. nitroglycerin; para. 0016, lines 1-4). Chwalisz et al. teach that endogenous nitric oxide levels can also be raised by L-arginine (nitric oxide substrate) treatment (para. 0016). Chwalisz et al. state that since nitric oxide is involved in numerous pathophysiological processes, it is theoretically possible to overcome some of the related to nitric oxide deficiency conditions with NO donors (page 2, last line to page 3, first three lines). Chwalisz et al. teach that the NO donors are mostly nonspecific and tolerance may be developed which limits their use (page 3, col. 1, first para., beginning at line 3). Chwalisz et al. teach NO donors, including nitroglycerin, and L-arginine analogues (e.g. NG-nitro-L-arginine methyl ester or L-NAME), glyceryl trinitrate, sodium nitroprusside, SIN-1, isosorbid mononitrate, and isosorbide dinitrate (page 3, col. 1, first para., beginning at line 3; and page 8, para. 0090).

Chwalisz et al. do not specifically teach the instant claimed Type II diabetes (e.g. claim 1), or the specific method steps recited in claim 21.

Herfindal et al. teach that diabetes is comprised of two major clinical conditions: type II maturity-onset, which represents about 80% of diabetics, and type 1 juvenile-onset, which represents only 15 to 20% of diabetic cases (page 308, col. 1, 2nd full para. to col. 2, first col.). Herfindal et al. state that most type II diabetics retain some pancreatic function and may be controlled by diet plus oral hypoglycemic drugs even though insulin may be required in 20 to 30% of type cases, while type I diabetics

require insulin to sustain life since they have no pancreatic function (page 308, col. 1, 2nd full para. to col. 2, first para.).

It would have been obvious to a person of skill in the art at the time the invention was made to treat a patient with diabetes mellitus, including a patient with Type II diabetes, with a therapeutically effective amount of a therapeutic nitric oxide donor compound, either singly or in combination (e.g. nitroprusside and/or SIN-1), to control the symptoms of diabetes. One would have been motivated to do so because Chwalisz et al. teach a method of treating diabetes mellitus comprising administering an effective amount of a nitric oxide donor compound (e.g. nitroprusside or SIN-1) which may be administered separately or in combination and therefore one would reasonably expect to preferentially treat a patient with Type II diabetes with an effective amount of a nitric oxide donor compound (e.g. nitroprusside or SIN-1) to control the symptoms of type II diabetes mellitus, as oppose to type I diabetes, and Herfindal et al. teach that type I diabetics require insulin to sustain life and that most type II diabetics do not require insulin therapy since they retain some pancreatic function and the NO donor drugs (e.g. SIN-1) as taught by Chwalisz et al. are not insulin drugs. Hence, one would expect to successfully treat a patient with Type II diabetes as taught by Herfindal et al. with a non-insulin type NO donor drug (e.g. SIN-1) as taught by Chwalisz et al. in view of the fact that the treatment of diabetes mellitus involves only two choices; namely, Type I and Type II diabetes mellitus, and only Type II diabetes mellitus is routinely treated with non-insulin drugs (e.g. nitroprusside or SIN-1) and both Chwalisz et al. and Herfindal. are concerned with the treatment of diabetes.

Further, it would have been obvious to a person of skill in the art at the time the invention was made to treat a patient with type II diabetes with a combination of two nitric oxide donor compounds (e.g. SIN-1 and sodium nitroprusside) for additive effects in controlling the symptoms of diabetes by administering said two nitric oxide donor compounds (e.g. SIN-1 and sodium nitroprusside) to the patient via any suitable pharmaceutical means, including administering one of the nitric oxide donor in a unit dosage injectable formulation comprising an effective amount of the drug (e.g. sodium nitroprusside) and sequentially administering an oral dosage formulation comprising an effective amount of the second nitric oxide), depending on the storage stability of the dosage form, the oral bioavailability of the drug and the pharmaceutical suitability of the drug for injectable/oral use, as well as the required dose amount, which would vary depending on patient factors as body weight and oral tolerance to the specific drug(s). One would have been motivated to do so because Chwalisz et al. teach nitric oxide donor compounds can be administered by unit dosage injectable formulation or oral dosage forms (0114; 0116-0117) and that combination of agents can be employed either continuously or sequentially (para. 0119, last two lines). Also, Chwalisz et al. teach that NO donors are mostly nonspecific and that tolerance may develop with said drugs which limit their use and therefore one would expect to successfully combine two nitric oxide donor compounds, wherein the first compound is administered in a unit dosage injectable formulation comprising an effective amount of nitric oxide donor for increasing insulin sensitivity and subsequently administering an oral dosage formulation comprising an effective amount of a nitric donor for maintaining insulin sensitivity for

additive effects absente evidence to the contrary. Besides, it is the examiner's position that it is routine to administer a bolus dose a drug via a unit dosage injectable formulation, for its immediate therapeutic effect, followed by the administration of the same or different drug via oral dosage form in patients who require long-term treatment and Type II diabetes mellitus is a chronic. In addition, the dosage form and the route of administration of drugs are routinely manipulated to optimize therapeutic effects and minimize side effects depending on the pharmaceutical characteristics of the specific drug since some drugs may better tolerated when administered by injection (e.g. drugs that cause stomach upset) while others may be better tolerated by patient when administered by mouth (e.g. drugs that cause pain on injection).

With respect to the preamble of claims 1 and 21, the prior art teaches the same instantly claimed nitric oxide donor compounds (e.g. nitroprusside and SIN-1) to treat the same population (diabetes mellitus) and therefore one would reasonably expect that administration of the same drug to the same population as taught by the prior art would also have the same therapeutic effects as claimed, including increasing insulin sensitivity in a mammalian patient.

Regarding claims 1, 21, and 22, Chwalisz et al. teach sodium nitroprusside and SIN-1 (para. 0090).

Regarding claim 2, Chwalisz et al. teach drugs suitable for oral administration (col. 0116).

Regarding claim 3, Chwalisz et al. teach drugs for parenteral application and parenteral drugs have to be injected for parental use (0114).

Regarding claim 19, the discussion of the preamble is incorporated by reference. Since the prior art teaches the same drugs to treat the same instantly claimed population (diabetes mellitus), one would reasonably expect that the method encompassed by the prior art would have the same therapeutic as the instant claimed therapeutic effects, including increasing hepatic sensitizing substance (HISS) dependent insulin sensitivity.

Regarding claim 21, Chwalisz et al. teach that nitric oxide donors can be administered as a separate unit dosage form (paras. 0118 -0119) and also teach oral dosage forms (e.g. tablets; para. 0116) and formulations for parenteral administration (para. 0117). Further, Chwalisz et al. teach nitroglycerin (which is a nitric oxide donor) for oral administration twice a day and nitroglycerin is also known to be available in an injectable dosage form such that one would reasonably expect that the oral dosage of the nitric oxide donor (e.g. oral nitroglycerin) would be administered separately from the parental dosage form of the nitric oxide donor (e.g. parenteral nitroglycerin) and since the oral and parenteral dosage forms as taught by Chwalisz et al. are intended to be administered at least once day one would also expect that each oral and parenteral dose would administered in a single unit dosage formulation. In addition, Chwalisz et al. suggest that combinations of agents can be employed either continuously or sequentially (para. 0119, last two lines), wherein the agents are administered in an effective amount (see reference claim 1). The instant claim also requires administration of an effective amount of an injectable dosage form of a nitric oxide donor (e.g. parenteral nitroglycerin or parenteral nitroprusside sodium), followed by administration

of an oral dosage form of a nitric oxide donor (e.g. oral nitroglycerin). Since the prior art teaches the same drugs to treat the same instantly claimed population (any patient), one would reasonably expect that the method encompassed by the prior art would exhibit the same therapeutic effects as the instant claimed therapeutic effects, including increasing insulin sensitivity and also maintaining insulin sensitivity.

Regarding claim 22, the above discussion of claim 21 is incorporated by reference.

Regarding claim 23, Chwalisz et al. teach sodium nitroprusside, which is a pharmaceutical salt of a nitric oxide donor (nitroprusside; para. 0090).

Regarding claim 24, Chwalisz et al. teach tablets and capsules (para. 0116).

Regarding claim 25, Chwalisz et al. teach nitric oxide donors are preferably administered at least once daily (para. 0119) and also teach tablet and capsule dosage forms comprising nitric oxide donors (para. 0116). Thus, it is the examiner's position that it would have been obvious to a person of skill in the art at the time the invention was made to administer more than one tablet or capsule comprising a nitric oxide donor as taught by the prior depending on the required dose of the nitric oxide donor, which would reasonably vary depending on patients factors such as age, body weight, the specific disease condition, and severity of the disease.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to applicant's argument

Applicant's arguments with respect to the rejections under 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

21 February 2009
/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611